Esophageal Pathology

Introduction

This lesson uses the anatomy, histology, and physiology learned in the last lesson to discuss the hodge-podge of esophageal (but otherwise unrelated) disorders. Disorders of anatomy—varices, Mallory-Weiss tears, Boerhaave's syndrome—are about bleeding and perforation. Disorders of physiology—achalasia, corkscrew esophagus, and scleroderma—are about motility and cause dysphagia (difficulty swallowing).

Disorders of histology—Barrett's metaplasia, adenocarcinoma, and squamous cell carcinoma—are about cancer. And finally, we conclude with esophagitis, which is a mish-mash of anatomy and histology.

Pathology of Esophageal Anatomy

Esophageal varices. In patients with cirrhosis—scarring of the liver—blood flow through the portal system can be compromised. This means that blood flow through the portal vein into the liver and out through the hepatic vein is reduced. Fluid builds up behind the liver in the portal vein. This hydrostatic pressure prevents drainage from the gut and can lead to ascites. The esophagus is drained by the left gastric vein, usually into the portal vein. But the web of veins of the middle esophagus connects to the web of veins of the lower esophagus. When that pressure backs up in the portal vein, the venous drainage can **shunt through the esophageal web**, resulting in **esophageal varices**. In the context of previously diagnosed cirrhosis, esophageal varices present with gastrointestinal bleeding. One cause of cirrhosis is alcohol. Alcohol is also what links the three pathologies of esophageal anatomy (at least on a licensing exam).

Mallory-Weiss tears. These are longitudinal **partial-thickness** lacerations of the mucosa near the GE junction secondary to severe vomiting. They are seen in someone who vomits, vomits again, vomits blood, vomits more blood, and then stops vomiting blood. It is usually self-limiting. However, if they have not yet stopped vomiting blood, there is no way to clinically distinguish it from another source of bleeding without endoscopy. On a licensing exam, there will be a patient with an increased risk of vomiting, such as **an alcohol binge** or **bulimia**.

Boerhaave's syndrome is caused by a full-thickness perforation, a transmural tear through the wall of the esophagus. The esophagus is in the posterior mediastinum. The lungs flank the mediastinum. Air is supposed to be in the airway (trachea, bronchi, alveoli) or the esophagus. Air should not be in the pleural cavity (that is a pneumothorax). Air should never be in the mediastinum. If there is a hole in the air- containing tubes (trachea or esophagus), then air will leak into the mediastinum. Although this can also occur in the setting of prolonged, severe retching (as in Mallory-Weiss tears), this is also a feared complication of endoscopic procedures. The dilation of esophageal strictures or even just biopsies can result in perforation. In order to see the esophagus, an endoscopist must insufflate air. That increases the pressure within the esophageal lumen. Boerhaave's syndrome presents with severe toxicity. There is no hematemesis, but rather fever, leukocytosis, and tachycardia. In addition, the findings of **subcutaneous emphysema** (crackly sensation upon pressing on the skin of the chest) and **Hamman's crunch** (each heartbeat causes the crunching of air) will be present. An X-ray will reveal air in the mediastinum. This is a surgical emergency.

Test-taking tip: A patient who has drunk a lot of alcohol in their life and now has alcoholic cirrhosis and a GI bleed has varices. An alcoholic who vomits a lot and presents with mediastinitis has Boerhaave's syndrome. A person who has an alcohol binge and vomits a lot and vomits blood has Mallory-Weiss. These are not the only ways these conditions can occur, but they have been tested this way in the past because of the "overlap" with alcohol consumption.

Pathology of Esophageal Swallowing—Dysphagia

The LES is opened by its relaxation (mediated by the vagus) while peristaltic waves push the food down (initiated by vagal stimulus). This is normally not perceived at a conscious level. If the patient can perceive it, the condition is called **dysphagia**—difficulty swallowing. If it hurts when swallowing, that is called odynophagia. Suspect esophageal dysphagia when the patient feels food get stuck below the clavicle (as opposed to oropharyngeal dysphagia, where the sensation is above the clavicle). Esophageal dysphagia can either be a motility disorder (a functional problem of the muscles or nerves) or a mechanical disorder (a structural problem due to something growing into the lumen). A **motility** disorder will have **dysphagia to both solids and liquids**—the machinery just does not work. A **mechanical** disorder will have **progressive dysphagia** to large solid foods and, eventually, liquids. The mechanical disorder is usually a product of something growing into the lumen. As it grows, fewer things fit through easily.

Mechanical disorders include cancers, strictures, and webs. We talk about cancers in the next section. Motility disorders are discussed here—achalasia, scleroderma, and esophageal spasm. Motility disorders are diagnosed using a barium swallow (to visualize the esophagus and LES) and manometry (to visualize the contractions of the different segments of the esophagus). Only for achalasia is a biopsy required to rule out malignancy.

Achalasia is too tight an LES. Achalasia is the result of lost or damaged myenteric plexus neurons. This results in a triad of **incomplete LES relaxation**, **increased LES tone**, and **aperistalsis of the esophagus**. The normal myenteric neurons that release VIP and NO—those that would relax the LES—are lost, yet the ACh signal persists. That is what gives both incomplete LES relaxation (fewer or no inhibitory neurons) and increased tone (fewer excitatory neurons are lost). When food is swallowed, it cannot pass into the stomach, causing distension of the proximal esophagus and the symptoms of dysphagia. The cause of **primary achalasia** (which is, in a sense, idiopathic achalasia) is unknown, but it can also involve degeneration of the vagus nerve or vagal nuclei. Many diseases cause **secondary achalasia** (achalasia physiology due to something else). The most classic is **Chagas disease**, an infection with *Trypanosoma cruzi*. An individual who traveled to an endemic area contracts an infection with the parasite. Then, over decades, the *T. cruzi* destroys the myenteric plexus. In Chagas disease (but not other secondary causes), the myenteric plexus of the intestine, colon, and uterus can be affected as well. **Achalasia-like** dysfunction (which is the same thing as saying incomplete secondary achalasia) is seen in diabetic neuropathy, infiltration by malignancy, amyloid, and sarcoidosis. Achalasia will present with a **"bird's beak appearance"** on a barium swallow. This is because of a tight LES (narrowing at the distal esophagus) and aperistalsis of the proximal esophagus (dilation of the proximal esophagus) Manometry would show increased tone at the LES with a failure to relax, and weakened contractions of the proximal esophagus. All achalasia diagnoses must receive an endoscopy with biopsy to rule out cancer that causes external compression of the esophagus, a condition called **pseudoachalasia**. The biopsy can confirm the loss of myenteric plexus neurons, confirm the presence or absence of T. cruzi in the muscle, and rule out malignancy. To treat the condition, we need to loosen up the LES. Medications that cause smooth relaxation (nitrates, calcium channel blockers) can be used, but they are really short-acting. There are endoscopic interventions, such as botulism toxin and pneumatic dilation, but the preferred method of treatment remains **resection of the diseased area—**a myotomy.

Scleroderma is too loose an LES. Scleroderma itself is discussed in greater detail in the Rheumatology module (Musculoskeletal: Rheumatology #4: *Other Rheumatologic Conditions*). In scleroderma, the LES smooth muscle is replaced by collagen. Collagen is scar. Scar does not move. If the LES becomes immobile scar, it cannot contract. An LES that fails to contract allows for the regurgitation of gastric contents. There can be either dysphagia or, more likely, refractory GERD. A barium swallow will appear normal, but stomach contents may be regurgitated. Diagnosis is confirmed by biopsy, but the absence of contractions can be seen on manometry, and biopsy is usually not necessary.

Esophageal dysmotility syndromes. Manometry can be used to divide esophageal dysmotility into three principal forms: nutcracker esophagus, diffuse esophageal spasm, and hypertensive lower esophageal sphincter. That level of detail is too far beyond the scope of Basic Sciences. So we want you to learn them all as the same diagnosis. Nutcracker esophagus (high amplitude, pain) is the same as **diffuse esophageal spasm** (uncoordinated simultaneous contraction that leads to a corkscrew on a barium swallow). Peristalsis is the sequential contraction of muscle such that the food bolus is propelled in one direction. This is coordinated by the vagus nerve. If a region of the esophagus suddenly contracts out of order, it disrupts the passage of the bolus, causing dysphagia. These contractions are **very high-amplitude contractions** that are so tight they cause **pain**. There will be **odynophagia** and **dysphagia,** specifically to **hot and cold liquids**. The first time a patient presents with an episode, and they report "crushing substernal chest pain that is relieved with nitroglycerin," the diagnosis can be none other than angina. After myocardial infarction and coronary artery disease are ruled out, and the patient continues to have paroxysmal symptoms, make the diagnosis of diffuse esophageal spasm with a barium swallow. It will show a **corkscrew esophagus**. Confirmation is made with manometry—measuring the contractions of the muscle. The treatment is the avoidance of triggers, use of nitrates, or use of calcium channel blockers.

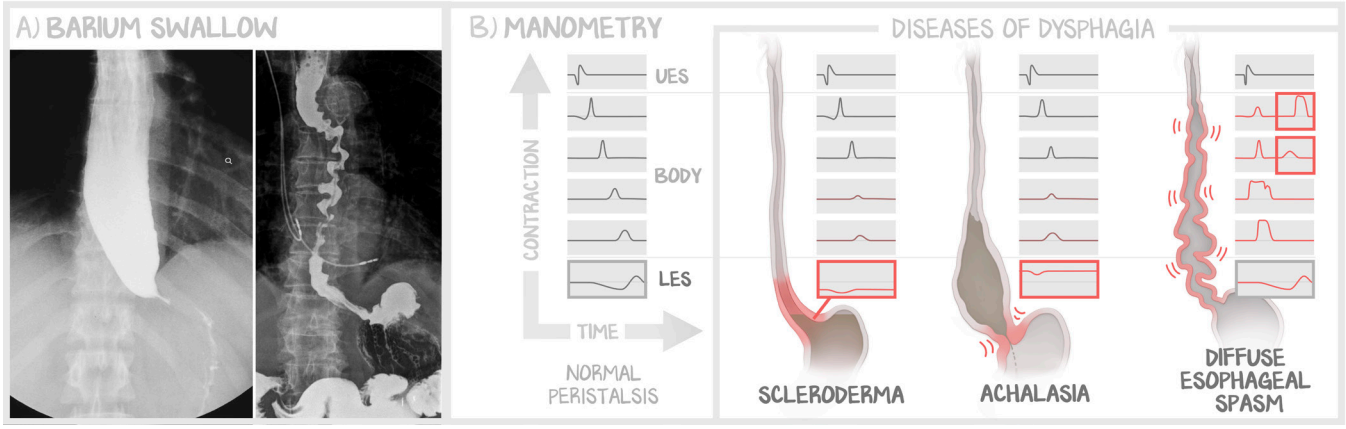

Figure 3.1: Diseases of Dysphagia
(a) Barium swallow showing a bird's beak deformity of achalasia. Next to it, a barium swallow of esophageal spasm.
(b) Characteristic esophageal manometry for each of the diseases discussed.

Pathology of Esophagus—Reflux to Cancer

GERD. Gastroesophageal reflux disease is when the **acidic contents of the stomach** reflux through the LES and **damage the esophagus**. Reflux is caused by either **transient LES relaxation** (normal relaxation in response to big meals or spicy foods that causes a little heartburn) or gross anatomic failures (abnormal relaxation that causes chronic or severe reflux). Those gross anatomic failures would be something like a **hiatal hernia** (where the stomach is already above the LES in the diaphragm) or a catastrophic LES disease like **scleroderma**. Most reflux comes in the way of transient relaxation.

Transient relaxation is what is described in commercials for reflux medications—a little burning in the back of the chest or a sour taste in the mouth, especially when eating spicy foods or too much food. A patient with GERD—with more than just transient LES relaxation every once in a while—will have daily symptoms. Symptoms include heartburn—**burning retrosternal pain** that is **worse when reclining** and **worse with acidic foods**, which thus improves **with sitting up and antacids**. Atypical symptoms are a **sour taste in the mouth**, **unexplained cough**, or **nocturnal asthma** (the acid damages the larynx while reclined, so it isn't actually asthma). Both GERD and transient LES relaxation are worsened by the **slowing of gastric emptying** (overeating or eating fatty meals) and behaviors that relax the LES (eating

chocolate, drinking **alcohol**, and smoking **cigarettes**). GERD without warning symptoms is empirically treated with either H2 blockers or proton pump inhibitors (although **proton pump inhibitors** have definitely overtaken H2 blockers in clinical practice, either is still acceptable). Lifestyle modifications to improve symptoms include weight loss, eating small meals, avoiding bad behaviors, and elevating the head of the bed. We go over those when we discuss stomach acidity pharmacology in GI: Digestion and Absorption: Start to Finish #5: *Physiology and Pharmacology of the Stomach*. GERD with warning symptoms for cancer (vomiting, anemia, weight loss) is diagnosed by EGD. Patients who fail empiric therapy get an EGD. GERD causes esophageal cancer, which is why it is in the esophagus lesson and not the stomach lesson. The EGD is to screen for cancer. Treat the GERD, prevent esophageal cancer. On endoscopy, GERD appears only as a reddened (inflamed) mucosa, if any change is noted at all. A biopsy of "only GERD" without progression towards metaplasia or dysplasia will reveal **basal zone hyperplasia** (increased stem cell proliferation in the stratum basale, representing stem cell activity to replace damaged tissue). Severe cases of "it's only GERD" will show **eosinophils** in addition to the basal zone hyperplasia (this becomes relevant for esophagitis below).

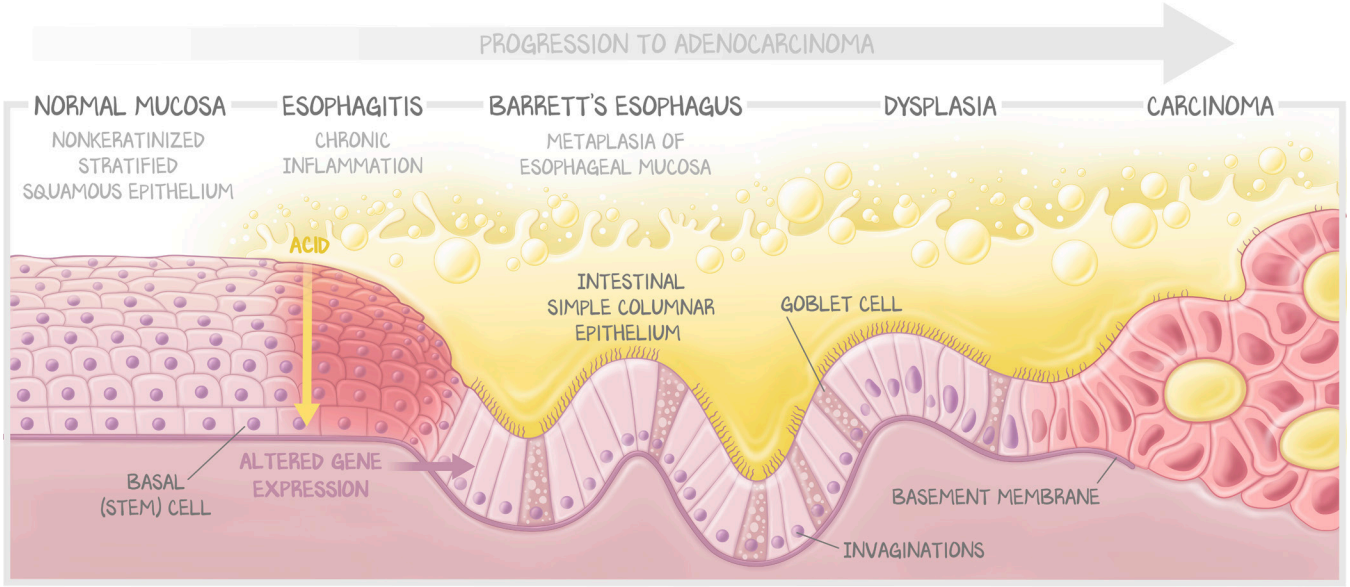

Figure 3.2: Progression to Adenocarcinoma
Normal stratified squamous epithelium progresses to adenocarcinoma in a well-elucidated manner. First, chronic inflammation due to acid reflux induces metaplasia to duodenal epithelium, which is tolerant of excess acid. That metaplasia requires an alteration of gene expression, vastly predisposing the tissue to the accumulation of mutations. Metaplasia leads to dysplasia. Left unchecked, dysplasia becomes carcinoma, proliferating and invading the basement membrane.

Barrett's esophagus is metaplasia of the esophageal mucosa. In the continuum between GERD and cancer lies Barrett's esophagus. Continual acidic damage to the mucosal epithelium induces a **metaplastic change** from the normal esophageal nonkeratinized stratified squamous epithelium to intestinal **columnar epithelium with goblet cells**. This change in tissue is a protective measure; the epithelium of the duodenum is able to tolerate the harsh acidity of the stomach. The esophageal stratified squamous epithelium is designed to protect it from debris; it is mechanical padding against the food bolus. The esophagus is supposed to be protected from acid by the LES. When it isn't, it changes its epithelium to one that can handle acid. The basal cells of the stratum basale are the stem cells that are programmed to make nonkeratinized stratified squamous cells. These basal cells can be induced by an acidic environment to alter their gene expression and become simple columnar epithelium that invaginates to form glands instead. You won't be surprised to hear that there are basal cells in the duodenal epithelium. But because it is a simple epithelium, the basal cells only punctuate the epithelium. Patients will state that they **had**

epigastric burning for decades, which then stopped spontaneously. Yay! They aren't burning anymore! But unfortunately, boo . . . metaplasia is precancerous. If there is Barrett's, there is a 50 times greater risk of progression to esophageal adenocarcinoma. Metaplasia, in general, is not always precancerous. Barrett's esophagus metaplasia is absolutely precancerous. Dysplasia and malignant transformation are on the way. On endoscopy, Barrett's appears as a **velvety, salmon-colored** epithelium that appears as if it's missing the white coating of the normal, stratified squamous epithelium.

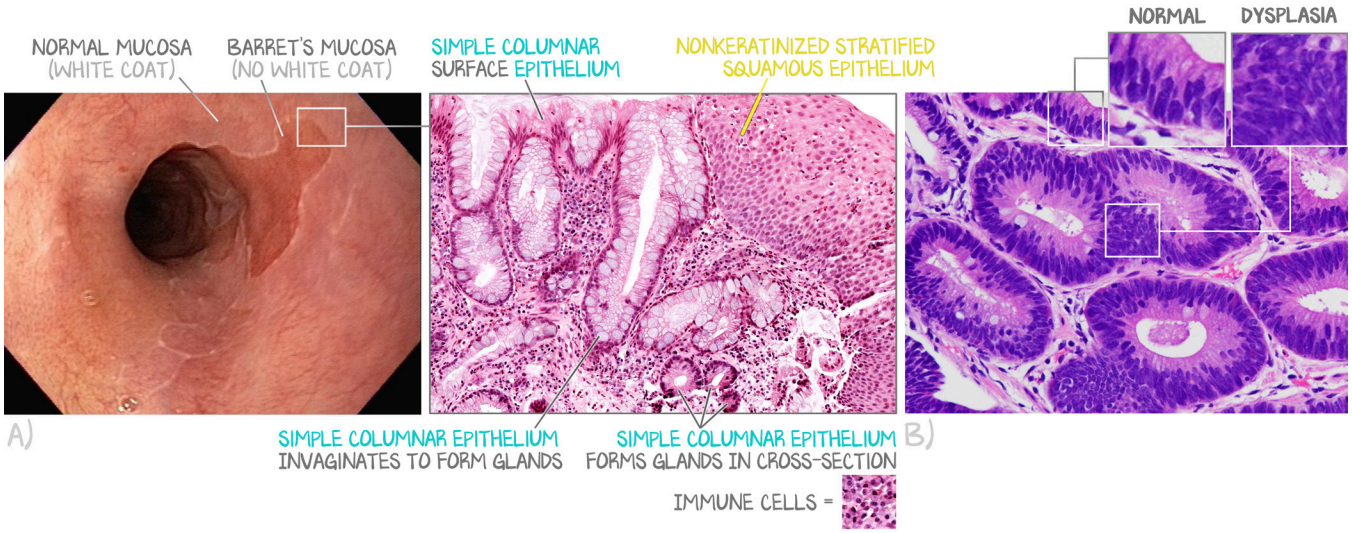

Figure 3.3: Barret's Metaplasia
(a) On endoscopy, the orange-pink-colored (salmon-colored) mucosa without the white coating is evidence of metaplasia. The regions of normal esophagus have a white coating that abruptly ends at the metaplastic areas. This example from early disease shows a great contrast between the abnormal and normal esophagus. The histology slide further demonstrates the abrupt change, showing normal, nonkeratinized stratified squamous epithelium immediately adjacent to the metaplastic, simple columnar epithelium that invaginates to form glands. Normal, non-mucinous columnar cells are identified at the surface of the invaginations, whereas the invaginations contain mostly mucin-secreting cells. (b) High-powered magnification of the mucosa demonstrating an invagination in longitudinal section, labeled "Normalish" as it represents the least dysplastic gland, and multiple dysplastic glands are seen in cross-section, thus appearing to be forming ducts (nuclei on the outside, cytoplasm towards the lumen). The nuclei are elongated, and most of the glands have added nuclei to what should be a simple epithelium.

Adenocarcinoma. Adenocarcinoma is the esophageal cancer of the Western developed world. It is caused by the development of intestinal metaplasia in the **lower third of the esophagus.** It is caused by GERD. Westerners tend to eat bigger meals, be bigger people, and have more GERD. The patient will describe really bad GERD that went away on its own (Barrett's). Then, as the cancer begins to grow into the lumen, it will cause dysphagia. The progressive growth will cause obstructive mechanical dysphagia with progressive symptoms, **first to large food boluses, then progressing to liquids**. These cancers can also bleed but will do so at a small trickle, resulting in insidious iron-deficiency anemia (which is why anemia is a warning symptom in GERD). A barium swallow will show an **asymmetric luminal narrowing** in the lower third of the esophagus. Biopsy reveals dysplasia of columnar epithelium. Because of the advent of proton pump inhibitors and the recognition of Barrett's esophagus (where intense PPI therapy or surgical intervention can prevent progression to cancer), the incidence of this cancer is falling. By the time the diagnosis is made without screening endoscopies, the cancer is beyond resection.

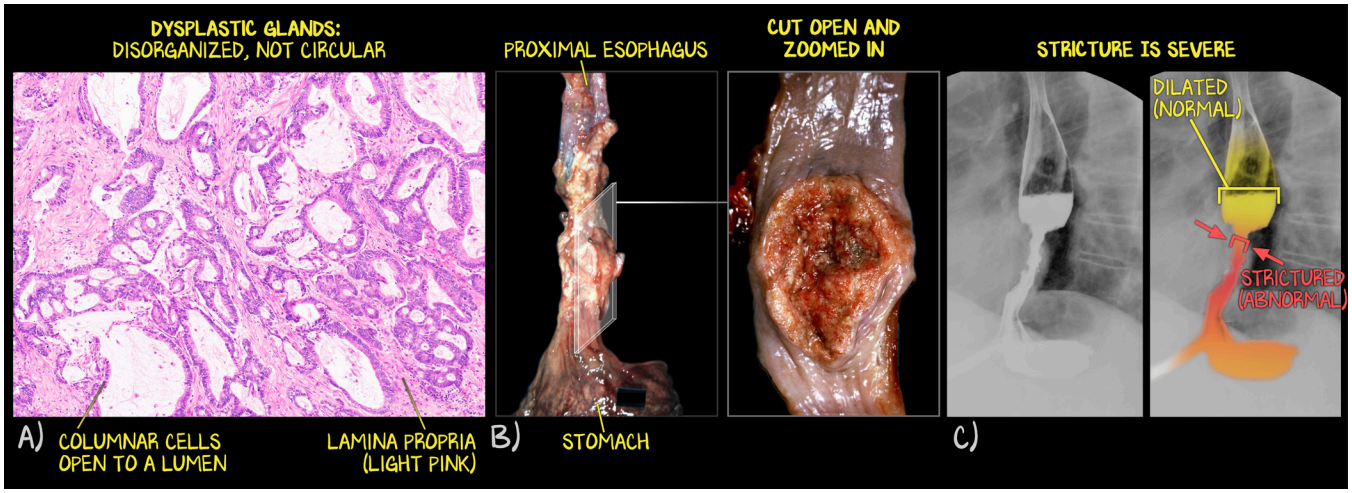

Figure 3.4: Esophageal Adenocarcinoma
(a) Moderate-magnification H&E-stained section showing multiple glands (simple columnar cells that line a lumen, appearing as ducts) in the lamina propria. The nuclei differ in size and shape, indicating advanced dysplasia. (b) Intact and dissected samples from a different case show a mass emanating from the distal esophagus, indicating it is likely adenocarcinoma. (c) An advanced stricture as identified by a filling defect in the distal esophagus.

Squamous cell carcinoma. Squamous cell carcinoma (SCC) of the esophagus is the leading esophageal cancer worldwide because the rest of the world either eats healthy or doesn't have access to food the way the West does. It occurs more often in impoverished communities and, even in high-risk regions (Iran, central China, Brazil, South Africa), the incidence varies substantially. There is less likely to be a progressive pattern or singular cause. Factors associated with increased risk are **cigarette smoking**, **alcohol use**, **HPV infection**, and **drinking very hot beverages**. All of these cause chronic inflammation. Inflammation leads to proliferation, proliferation to the acquisition of mutations. **Cigarettes** are universally accessible, as is **alcohol**. **HPV** infects any nonkeratinized stratified squamous epithelium, so the same HPV that causes cervical cancer can cause throat cancer (where semen goes, HPV goes). With vaccination against HPV, because the same strains that cause cervical cancer cause esophageal cancer, this risk factor can be eliminated. Drinking very hot liquids causes recurrent mild thermal burns, burns that heal but are still examples of inflammation. Some texts have used this fact to suggest that **cultures that drink hot tea** (Asia and the Middle East) are at the highest risk. However, it is less likely to be regional or cultural, but individual accumulation of risk. The presentation will be identical to that of adenocarcinoma, except there won't be any GERD. The work-up will include a barium swallow, showing **asymmetric luminal narrowing** in the upper third of the esophagus. A biopsy will reveal squamous cells. The cancerous nonkeratinized stratified squamous epithelium may produce keratin as skin cancers do. Keratinization of esophageal mucosa is highly suggestive of cancer. The treatment and prognosis are just as poor as for adenocarcinoma.

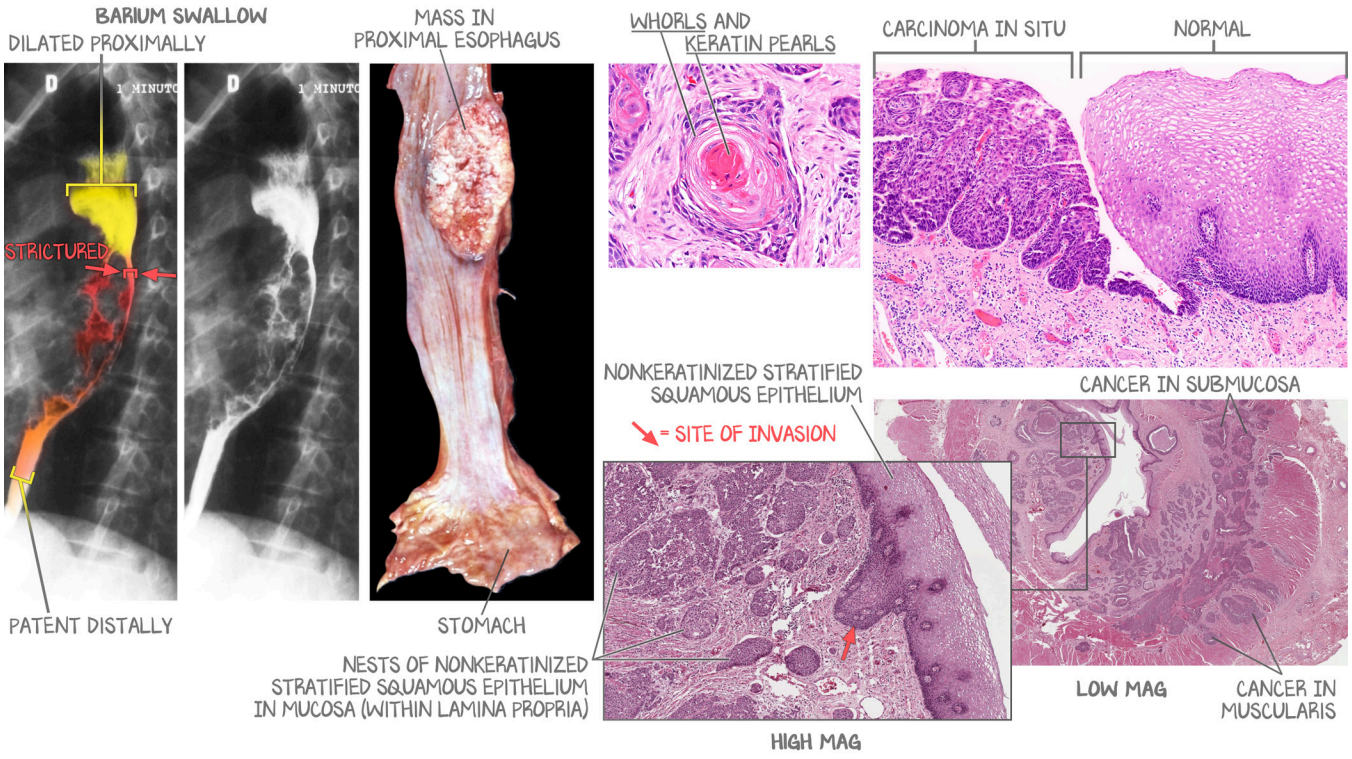

Figure 3.5: Esophageal Squamous Cell Carcinoma
The barium swallow shows a dilated proximal esophagus, a normal patent distal esophagus, and a large stretch of the mid esophagus, where the contrast barely shows a trace lumen. On gross, the squamous cell carcinoma is proximal, far from the stomach, indicating a proximal cancer. On histology, the micrograph showing carcinoma in situ next to the normal epithelium was achieved by focusing on the cancer margin. Beneath that field were examples of whorls and keratin pearls. At low magnification, this invasive carcinoma can be seen in the muscularis externa, submucosa, and lamina propria of the mucosa. On higher magnification, the nests within the lamina propria demonstrate a stratified squamous phenotype.

Esophageal Pathology: Esophagitis

A PIECE of the esophagus is the mnemonic we teach in the clinical course: Pill induced, Infectious, Eosinophilic, Caustic ingestion, and Everything else (for GERD). For the Basic Sciences, it is much higher-yield to focus specifically on the **infectious causes** and **eosinophilic** only. But recognize that if a pill gets stuck, it can erode the esophagus (pill-induced). If someone drinks lye or eats a battery, caustic damage to the esophageal lining may occur. These fall much easier into the diagnosis and management questions designed for the clinical years.

"PATHOGEN"	EXAM FINDING	ENDOSCOPY/MICROSCOPY	TREATMENT
CMV	Retinitis, colitis Odynophagia	Endoscopy: Large shallow **linear ulcerations** Micro: Cytoplasmic and intranuclear inclusions, **owl's eyes**	Ganciclovir
HSV	Oral ulcers Odynophagia	Endoscopy: **Punched-out** ulcers and **vesicles** Micro: **Multinucleated giant cells** and eosinophilic intranuclear inclusions (Cowdry bodies)	Acyclovir
Candida albicans	**Oral thrush** AIDS-defining illness Odynophagia	Endoscopy: Patches of white-colored pseudomembranes adherent to the mucosa Micro: Yeast cells and pseudohyphae invading mucosa	Fluconazole
"Eosinophils"	Asthma, allergies, and atopy	Endoscopy: GERD with Rings Micro: ≥ 15 eosinophils/HPF After trying to treat GERD as GERD	PO inhaled steroids

Citations

Figure 3.1: Courtesy of Matthew Parker, MD.

Figures 3.3, 3.4a: Courtesy of WebPathology.com.

Figure 3.4b: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.

Figure 3.4c: Courtesy of Radiopaedia.org.

